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DN 125:300822
TI Preparation of N-**chromanyl** and N-**chromanylmethyl** 2-amino-1-phenylethanol compounds as adrenergic β3-receptor stimulants
IN Tsucha, Susumu; Fukuzaki, Atsushi; Takenawa, Noriko; Ozaka, Kazuya
PA Tokyo Tanabe Co, Japan
SO Jpn. Kokai Tokkyo Koho, 10 pp.
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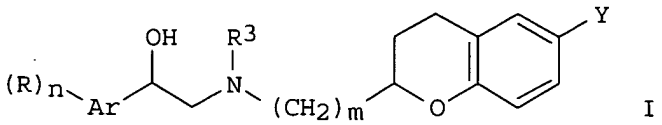

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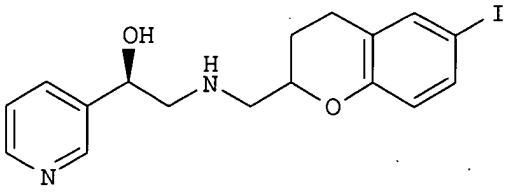

II

AB This invention relates to novel 2,6-substituted **chroman** derivs. which are useful in the treatment of **.beta.3-adrenoreceptor** mediated conditions. Title compds. I [wherein R = independently OH, :O, halo, CN, NO2, (halo)alkyl, CF3, NR1R1, SR1, OR1, SO2R2, OCOR2, NR1COR2, COR2, NR1SO2R2, or (un)substituted Ph or heterocyclyl; R1 = independently H, (CH2)mO(CH2)mR5, or (un)substituted (cyclo)alkyl, Ph, or naphthyl; or NR1R1 = heterocyclyl; R2 = independently R1, OR1, NR1R1, or (un)substituted NHSO0-2-Ph, NHSO0-2-naphthyl, NHSO0-2-alkyl, or heterocyclyl; R3 = H, alkyl, or COR3; R4 = H, alkyl(phenyl), or alkylpyridyl; R5 = H or CO2H; R6 = H or (un)substituted alkyl or alkyl-SO0-2-alkyl; Ar = Ph or (fused) hetero(aryl); Y = halo, NO2, R6, SR1, SO0-2C6H4CO2R1, (CONR4CR4R4)pCO2R1, or (un)substituted Ph or heterocyclyl; m = 1-3; n = 0-5; p = 1 or 2; and pharmaceutically acceptable salts and esters thereof] were prepared as β **3-adrenoceptor** agonists. For example, coupling of (2R)-6-iodo-3,4-dihydro-2H-chromene-2-carboxylic acid and (1R)-2-amino-1-(3-pyridinyl)ethanol•2HCl with 1-hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide•HCl, and TEA in CH2Cl2 gave the amide (74%). Reduction using borane-dimethylsulfide complex in THF afforded the **chromanmethaneamine** II (84%). Over one hundred compds. of the invention demonstrated **.beta.3-adrenergic** receptor agonist activity with EC50 values ≤ 1μM. I are useful in the treatment of **.beta.3-adrenergic** receptor mediated conditions, including obesity, diabetes, **gastrointestinal** disorders, cardiovascular disorders, and urinary disorders (no data).